Journal of Medical Virology 54:158–161 (1998)

Herpes Simplex Virus-1 and Varicella Virus Infections in Familial Dysautonomia Patients

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Familial dystautonomia (FD) patients are deficient in type C fibers, suggesting that there may be a different pattern of infection and clinical presentation when infected by Herpes simplex virus type 1 (HSV-1) or Varicella-Zoster virus (VZV). These viruses infect and are reactivated in the periphery of the body through type C sensory nerve fibers. HSV-1 infects epithelial cells, penetrates into type C fibers, and migrates to the ganglia to generate latent infection. In reactivation, the viral DNA migrates through type C fibers, infecting the epidermis at the entry site. VZV infects through the respiratory tract, causing systemic viral infection and latency in the ganglia, from which it is reactivated and reaches the skin. The study was carried by clinical questionnaire and by HSV and VZV IgG antibodies on fifty-one FD patients and eighty matched controls. The questionnaire revealed that no FD patient had a history of clinical HSV-1 infection, compared to 15% in the control group ($P < 0.05$), while 50% FD patients had been infected by varicella, compared to 66% in the VZV control group. However in FD, VZV clinical manifestations were mild in comparison to controls. There was no difference in infection rates for some other viral diseases. HSV-1 antibodies were detected in 24% of the FD patients, compared to 38% in the control group ($P < 0.1$). VZV antibodies were similar in FD and controls (66%, 63%). We concluded that the rate of HSV infection in FD is low and clinical reactivation is rare. The rate of varicella infection appears to be the same for patients and controls, but in FD the clinical presentation is mild. We suggest that these differences are due to the lack of type C fibers in FD patients. ***J. Med. Virol. 54:158–161, 1998.***

KEY WORDS: HSV reactivations; VZV infections; type C (nonmyelinated) fibers

INTRODUCTION

Familial dysautonomia (FD) or Riley-Day Syndrome [Riley et al., 1949; Axelrod and Pearson, 1984] is an autosomal disorder affecting autonomic, sensory, and motor functions. The syndrome is limited to Ashkenazi Jews and the defective FD locus was recently mapped [Blumenfeld et al., 1993] to chromosome 9q31-q33. FD patients are affected from birth with a variety of symptoms: the main ones are gastrointestinal dysfunction, leading to recurrent aspiration with repeated pneumonia and chronic lung disease. FD is characterized by an altered sensitivity to pain and temperature in various areas of the body. There is a lack of overflow tears, diminished or absent tendon reflexes and reduced fully-formed papillae in the tongue, as well as orthopedic, neurological and cardiovascular instability problems [Axelrod, 1995]. There is failure to induce an axon flair following intradermal histamine which is an indicator for peripheral neuropathy. Pathological studies reveal a decrease in the size of sympathetic and parasympathetic ganglia and the number of their neurons resulting in a decrease in the number of postganglionic nerve fibers. A decrease in the number of cholinergic and adrenergic nerve fibers innervating peripheral blood vessels was observed [Grover-Johnson and Pearson, 1975]. Peripheral sural nerve biopsies from FD patients showed a marked decline of nerve axons designated type C fibers and a decrease in myelinated fibers [Pearson et al., 1975]. The marked decrease in the number of type C neurons and axons may be related to altered sensitivity to pain in FD patients. Anatomical absence of substance P (SP) containing neurons was noted in substantia gelatinosa in the spinal cord and brain stem of FD patients [Pearson et al., 1982].

The marked decline in SP-containing neurons in FD patients and the peripheral neuropathy had lead us to question whether Herpes simplex virus-1 (HSV-1) is

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Accepted 15 October 1997

TABLE I. Prevalence of IgG Antibodies to HSV-1 and VZV in Patients with Familial Dyautonomia (FD) and Healthy Controls

	Patients (total 51)		Controls (total 80)	
	HSV Ab*	VZV Ab*	HSV Ab	VZV Ab
Age				
0–2	0/6 (0%)	0/6 (0%)	3/12 (25%)	4/12 (33%)
3–6	4/14 (28%)	5/11 (45%)	5/24 (21%)	12/24 (50%)
7–10	2/11 (18%)	7/11 (64%)	9/20 (45%)	16/20 (80%)
11–16	2/8 (25%)	7/8 (88%)	5/10 (50%)	10/10 (100%)
>16	4/12 (30%)	11/12 (92%)	8/14 (60%)	11/14 (80%)
No.	12/50 (24%)**	33/51 (66%)	30/80 (38%)**	53/80 (63%)

*HSV-Ab, VZV-Ab = IgG antibodies to herpes simplex type 1 and varicella-zoster virus respectively.
**$P < 0.1$.

capable of infecting the trigeminal ganglion (TG) in FD children and whether reactivation of HSV-1 in such patients is possible. It was reported [Ljungdahl et al., 1986] that mice which were treated at neonatal age with capsaicin, the pungent agent of hot pepper, manifested loss of chemosensitive pain as well as degeneration of small size type C sensory neurons. Some of these neurons contain SP and also calcitonin gene related peptide (CGRP). These investigators suggested that the degenerative effect of capsaicin on central branches of SP containing sensory nerves may contribute to the deafferentiation pain syndrome following HSV infection. It was also noted [T. Ben-Hur and Y. Becker, unpublished results] that HSV-1 ocular infection and mortality of capsaicin-treated mice was reduced when compared to HSV-1 ocular infection in untreated infected mice. Thus the absence of type C fibers in capsaicin treated mice and the higher resistance of such mice to HSV-1 infection, suggests that type C fibers are the port of entry of HSV-1 from the peripheral site of infection into the mouse nervous system. Hence we hypothesized that a reduced HSV-1 infection rate may be expected in FD patients.

Thus HSV-1 infections in FD patients could serve as a marker for the absence of peripheral type C fibers which connect to the CGRP/SP neurons in ganglia and brain. The aim of the present study was to evaluate the clinical signs of Herpes group viruses in FD patients, and to detect those patients who were infected with HSV-1 and Varicella Zoster virus (VZV) by testing for anti-viral IgG antibodies.

MATERIALS AND METHODS

Fifty-one FD patients and 80 healthy controls matched for age, sex, origin and family size were included in the study. All the FD patients were diagnosed by the specific symptoms and signs [Axelrod, 1995], by a pathological histamine test, and by the specific FD genetic markers which are located on chromosome 9 [Blumenfeld et al., 1993]. Clinical data concerning the morbidity of FD patients, with Herpes group and other viral infections, were collected from individual questionnaires and medical files of the participants. The clinical questionnaire included questions on the past history of several viral diseases, based on clinical description and/or documentation, and data of prior vaccination against some viral infections. It also included evaluation of the number and shape of the observed lesions and accompanying symptoms, including fever, nausea, vomiting, myalgia or corysa, cough, headache, dizziness, conjunctivitis and other clinical manifestations like stridor, meningitis and pneumonia. Demographic data included number of family members, crowding at home, and parents' profession.

The following diseases were surveyed: chicken-pox, measles, rubella, mumps, infectious mononucleosis, herpes labialis (primary or recurrent), influenza-like infections (as an indicator for common cold and other upper respiratory tract infections). Clinical blood samples of each group were matched and tested for the determination of IgG antibodies to HSV and VZV by the Enzyme Linked Immunosorbent Assay (ELISA) method (for HSV-Cobas Core, Roche, Switzerland. For VZV-Enzygnost, Behring, Germany). We compared the data for IgG titers to HSV-1 and varicella for the two groups. The result was considered positive when the antibody titer was above 1:40 (according to the lowest dilution of the ELISA instructions). Statistical analysis was done by Chi square test.

RESULTS

The data of 51 patients and 80 matched controls, including the prevalence data of IgG antibodies to HSV-1 and VZV, are summarized in Table I. Seropositivity to HSV-1 was found in 24% of FD patients while in controls it was 49%. The difference was significant at $P < 0.1$. At the same time no significant difference was observed in seropositivity to varicella zoster virus (VZV IgG antibodies) between the FD patients (63%) and controls (66%), but it is emphasized again that the clinical course was different, with FD patients being only mildly effected.

Analysis of the questionnaires (Table II) showed that in patients with FD not one episode of clinical HSV infection was noted, as compared with twelve out of eighty (15%) in controls ($P < 0.05$). Fifty percent of patients and 66% of controls, had a history of chicken-pox (Varicella Zoster). All the FD patients had a very mild clinical picture with only a few vesicles.

When the incidence of other viral diseases was clini-

TABLE II. Incidence of Common Viral Diseases in Patients and Controls According to Clinical Questionnaires

Disease	Familial dysautonomia	Controls
Oral herpes* (Reactivation)	0/40 (0%)	12/80 (15%)
Chickenpox	20/40 (50%)	53/80 (66%)
Influenza	33/40 (84%)	72/80 (90%)
Measles	6/40 (15%)	8/80 (10%)
Mumps	12/40 (30%)	32/80 (40%)
Rubella	6/40 (15%)	24/80 (30%)
Infectious Mononucleosis	0/40 (0%)	4/80 (5%)

*$P < 0.05$.

cally compared (Table II), there was a similarity between FD and controls in influenza (84%, 90% respectively), measles (15%, 10% respectively), and infectious mononucleosis (0%, 5% respectively). There was a bigger difference with mumps (30%, 40% respectively) and rubella (15%, 30% respectively).

The effect of age on the extent of HSV-1 seropositivity in FD and controls was compared (Table I). There were no IgG antibodies to HSV-1 in FD patients until 2 years of age. HSV-1 seropositivity occurred in 28% of the FD patients between the ages of 3 to 6 years. FD patients older than 3 years of age showed no increase of HSV seropositivity with age while in the control group there was a gradual increase in the number of HSV-1 seropositive children. Twenty-five percent of the healthy control group were infected by HSV-1 until 2 years of age, 45% at ages of 7 to 10 years, and up to 50% at ages 11 to 16 years. At ages 16 to 34 years, 60% of the controls were already infected with HSV-1.

A similar situation was noted for VZV antibodies. FD patients did not have any anti-VZV antibodies between 0–2 years of age, while 33% of healthy children were seropositive. In contrast to HSV-1, no gross serological differences were observed with age in the case of VZV antibodies. In the FD group, at age of 3–6 years 45% were infected with VZV, and at the age of more than 16 years 92% had IgG antibodies to VZV. In the control group, at 0–2 years of age, 33% had VZV antibodies which gradually increased to 100% at the ages of 11–16 years.

DISCUSSION

In this study the extent of HSV and VZV viral infections in FD patients was examined. A significantly lower rate of HSV antibodies was found in a retrospective study of FD patients as compared to matched healthy controls, and no clinical skin signs of HSV infections in FD patients. The prevalence of VZV infections was the same in both groups, with a milder clinical course in FD patients. It could be that the reduced number of type C fibers in FD patients effects the clinical situation due to the inability of the peripheral C fibers to serve as port of entry.

The port of entry for VZV is the respiratory tract, however HSV-1 ports of infection in the nervous system are type C nerve endings in the skin epithelium and the mucous membranes of the mouth, eye and nose. Type C fibers responses are decreased in FD patients, therefore the ability of HSV-1 to enter the nervous system in FD patients might be limited. This might explain the lack of difference in seropositivity in controls and FD patients (66% and 63% respectively). However the mild clinical course with very few vesicles on the skin of FD patients can be explained by the reduced C fibers. The absence of clinical reactivations of oral HSV in FD patients as compared to clinical reactivation of oral HSV in 15% of healthy children ($P < 0.05$, Table II), suggests the difficulty of HSV to reach and establish latency in a ganglion. Since HSV-1 may infect and replicate in epithelial cells and since the immune response in FD patients is unaffected, titers of IgG antibodies to HSV-1 can be detected in 24% of the FD group as compared to 38% in the controls.

This assumption can explain another finding of this study which shows absence of antibodies to HSV and VZV in FD children aged 0–2 years while in healthy controls of the same age 25% were found to have HSV antibodies and 33% with VZV antibodies (Table I). HSV antibodies were detected in FD patients at later ages only up to 30%, while in the control group there was a gradual increase in the number of infected individuals up to 60%. This could provide a clue as to the state of type C neurons and fibers in these children which is connected with the development of the clinical aspect of the FD disorder with a progressive sensory loss over the years [Axelrod et al., 1981]. For VZV infections there was a gradual increase of up to 92% in the FD group, and 100% in the controls.

In the presence of type C fibers which contain CGRP and SP [Yamamoto and Tohyama, 1989], oral HSV in infected healthy individuals is transported into the ganglia and brain. When type C fibers are decreased as in FD patients, transport, latency and reactivation of HSV appears to be difficult. The only alternative route for HSV infection in FD patients may be through the nasal ciliary olfactory nerve epithelium and the olfactory nerve, which lack type C fibers, but constitute a nerve route from the olfactory bulbs, locus coerelus, amygdala and hippocampus in the brain [McLean et al., 1989]. The extent of HSV infections by the nose-brain route in FD patients is not known, but one FD patient with HSV-1 encephalitis was diagnosed. [Ch. Maayan, unpublished]. It could be that some clinical aspects of FD may be explained by the lack of release of CGRP [Poyner, 1992], due to the defect in type C fibers innervating systemic organs.

It is concluded that FD patients are better protected from HSV-1 infection and from VZV clinical symptoms than the healthy individuals. We suggest that these differences are due to the decreased type C fibers in FD patients and their progressive sensory loss. HSV infections in FD could serve as a marker to the decreased type C fibers which connect to the CGRP/SP neurons in the ganglia and brain.

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